REMARKS

Objections

Sequence Listing

Applicants filed on January 5, 2011 by Express Mail a computer-readable form of the Sequence Listing as requested by the Examiner with a statement that the Sequence Listing information recorded in computer readable form is identical to the written (paper/compact disc) Sequence Listing.

35 U.S.C. §112 First Paragraph Rejections - Enablement

The Examiner has maintained the rejection of claims 50, 64-67 and 74-76 under 35 U.S.C. §112 first paragraph and extended this rejection to newly submitted claims 77-80.

In presenting this rejection the Examiner indicated that the factors to consider to determine if the disclosure satisfies the enablement requirement and whether any experimentation is undue are the factors identified in *In re Wands*, 858 F.2d 731, 737, 8 USCQ 2d 1400, 1404 (Fed. Cir. 1988).

Applicants respectfully traverse this rejection and provide the following comments regarding an *In re: Wands* analysis. In the discussions which follow, Applicant will refer to paragraph numbers in the published application No. US2005/0226879 A1.

The Nature of the Invention

Certain aspects of the present invention are directed to methods of inhibiting the cell cycle of a cell. The methods comprise administering a Nup153 inhibitor to a cell. Nup153

inhibitors inhibit nuclear envelope breakdown by inhibiting the activity of the nuclear pore protein Nup153. Nuclear envelope breakdown is a critical step in the cell cycle. By preventing nuclear envelope breakdown the cell cycle can be inhibited. Cancerous cells which require rapid cell division are particularly susceptible to inhibition of the cell cycle accordingly, Nup153 inhibitors may be used to treat/prevent the growth of cancer cells.

Breadth of The Claims

The currently pending independent claims, claims 50 and 77 read as follows:

> 50. A method of inhibiting a cell cycle of a cell comprising administering a Nup153 inhibitor to the cell, wherein the Nup153 inhibitor inhibits the cell cycle of the cell, wherein the Nup153 inhibitor is a peptide.
>
> 77. A method of inhibiting a cell cycle of a cell comprising administering a Nup153 inhibitor to the cell, wherein the Nup153 inhibitor inhibits the cell cycle of the cell, wherein the Nup153 inhibitor interferes with a Nup153-COPI interaction.

Accordingly, Claim 50 and the claims which depend on Claim 50 are directed to methods which utilize inhibitors which are peptides. Claim 64 depends on Claim 50 and recites that the cell does not proceed through cell division. Claim 65 depends on Claim 64 and recites the cell does not undergo mitosis. Claim 66 depends on Claim 64 and recites the cell is inhibited during interphase. Claim 67 depends on Claim 50 and recites the cell is a cancer cell. Claim 80 depends on Claim 50 and recites the Nup153 inhibitor interacts with the zinc finger region of Nup153.

Claim 77 is directed to methods in which the Nup153 inhibitor interferes with a Nup153 – COPI interaction. Claim 78 depends from Claim 77 and recites wherein the Nup153 inhibitor

directly or indirectly interferes with a Nup153-COPI interaction. Claim 79 depends from Claim 77 and recites wherein the Nup153 inhibitor interacts with the zinc finger region of Nup153. Accordingly, Claim 77 and the claims which depend on Claim 77 are directed to methods that utilize inhibitors that interfere with a Nup153 – COPI interaction.

The State of the Prior Art

At the time of the invention, it was known that cells undergo mitosis to reproduce and that the nuclear envelope dissolves in prophase [paragraphs 0019-0022]. It was also known that cancer arises from a loss of normal cell growth control and that chemotherapeutic agents such as Taxol® and vinblastine, which interfere with steps in cell division, can be used to treat cancer. Techniques for making compounds such as proteins, peptides and nucleic acid based compounds were known in the art.

Using *Xenopus* egg extracts to study mitotic spindle assembly and function *in vitro* was a known and well accepted model system. See for example Methods in Cell Biology, Volume 61, 1998, Pages 385-412, Chapter 20 The Use of *Xenopus* Egg Extracts to Study Mitotic Spindle Assembly and Function *in vitro*. (Copy enclosed)

The Level of Predictability

Predictability refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention (MPEP 2164.03). The presently disclosed results demonstrate Nup153 inhibitors inhibit the breakdown of the nuclear envelope. The claimed invention is directed to methods for inhibiting the cell cycle of a cell using a Nup153 inhibitor.

For a cell cycle to occur there must be breakdown of the nuclear envelope. The presently disclosed results predictably demonstrate that inhibiting breakdown of the nuclear envelope directly inhibits the cell cycle of a cell. Examples 1 and 2 of the present application present clear guidance on how to prepare inhibitors and test these inhibitors for the ability to inhibit the breakdown of the nuclear envelope and this inhibition of nuclear envelope breakdown is directly associated to the inhibition of the cell cycle.

The Existence of Working Examples

Applicants provided working examples 1 and 2 in the specification. As the Examiner has acknowledged, these examples teach incubation of Nup153 fragments in example 1, or synthetic peptides in example 2, with cell free extracts derived from *Xenopus* eggs and that the administration of these inhibitors to Nup153 inhibited the breakdown of the nuclear envelope.

The specification identifies a nucleic acid and peptide sequence for Nup153 [see paragraph 0056 and SEQ ID Nos. 1 & 2] and further identifies structural regions of Nup153 in particular the zinc finger domains to aid in preparing inhibitors. The specification also identifies methods for screening and identifying inhibitors [paragraphs 0267-0289] including the working examples.

In presenting the enablement rejections the Examiner has focused on an *in vitro/in vivo* correlation. The MPEP § 2164.02 discusses the *in vitro/in vivo* correlation stating:

> "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention... if the art is such that a particular model is recognized as correlating to a

> specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate."

Working Example 1 presents an *in vitro* model demonstrating that a fragment of Nup153 encompassing the central zinc finger domain of Nup153 provided a striking inhibition of nuclear envelope breakdown. [See paragraph 0317] . Example 1 included studies using HeLa cells (a well-studied immortalized cervical cancer cell line) and cell-free extracts derived from *Xenopus* eggs to investigate the interrelation between COPI and Nup153.

Models using *Xenopus* egg extracts are recognized as correlating to a specific condition since studies using *Xenopus* egg extracts *in vitro* are widely used to study the cell cycle including cancer and potential treatment options.

Applicants have provided two publications (Salisbury, et al., and Chang, et al.) to demonstrate the use of *Xenopus* systems to study cancer. These papers discuss studies using *in vitro Xenopus* egg assays in study of tissue sections from cancer patients. See Microtubule Nucleating Capacity of Centrosomes In Tissue Sections, Salisbury, et al., (The Journal of Histochemistry & Cytochemistry, 1999 47(10) 1265-1273). Additionally, as shown in Chang, et al., Synthesis and Biological Evaluation of Myoseverin Derivatives: Microtubule Assembly Inhibitors (Journal of Medicinal Chemistry, 2001 44:26, 4497-4500), *Xenopus* egg assays were used to screen compounds for inhibition of spindle assembly followed by testing against 60 cancer cell lines. Accordingly, Applicants submit that the *in vitro* studies presented in the application using *Xenopus* egg extracts correlate with the claimed methods since over the years

Xenopus model systems have become recognized as relevant to the study of the cell cycle including the cell cycle in human cancers.

A recent review article also supports the use of *Xenopus* as a model system for studying cancer. See Learning About Cancer From Frogs: Analysis Of Mitotic Spindles In *Xenopus* Egg Extracts (Cross MK, Powers MA, Dis Model Mech. 2009 Nov-Dec; 2(11-12):541-7). PMID: 19892884. (Copy enclosed) As stated in this paper "Much that has been learned from *Xenopus* extracts about cell cycle regulation, DNA replication and repair, and spindle assembly and function is proving to be relevant to human cancers." (see page 545)

In presenting the arguments that the *in vitro* results are not sufficient to support enablement the Examiner has cited Frantz. In the first instance, Frantz does not address the PTO requirements for enablement but instead is directed to the decline of *in vivo* pharmacology studies by other methods including *in silico* studies. A close reading of Frantz shows it is a general article on the need for more *in vivo* pharmacology studies and pharmacologists to do these studies.

The Kamb and Roberts et al. publications cited by the Examiner are directed to problems with the predictive abilities of cancer models and clinical trials. Applicants submit that the studies in Kamb and Roberts, et al., are relevant to the FDA and not the PTO enablement requirements. The PTO requirements for enablement are different from the FDA requirements for saftety and efficacy for human therapeutic use. As described below the PTO has provided guidance as to *in vitro* and *in vivo* correlations. There is no PTO requirement that Applicants provide clinical study data for a compound to demonstrate enablement.

The Amount of Guidance or Direction

The Examiner has argued that the specification provides insufficient guidance and objective evidence to predictably enable the use of the claimed methods *in vivo*. Applicants submit the present application provides considerable guidance and direction on how to practice the invention. The nature of interference with the Nup153-COPI interaction is described in detail [paragraph 0036]. Furthermore, important structural regions of Nup153 are identified; in particular the importance of the N terminal and C terminal regions surrounding the zinc finger regions and the zinc finger region itself is described [paragraphs 0044 to 0061], including embodiments that may include multiple zinc fingers linked together.

Applicants describe a fragment of Nup153 encompassing the central zinc finger domain of Nup153 in Example 1 which inhibited nuclear envelope breakdown. The application provides extensive disclosure on how to make and use compounds of the present invention at least in Applicants' description of: the variants of the Nup153 protein and derivatives of these proteins [paragraph 0140]; and the variety of other forms of inhibitors, including chimeric proteins [paragraph 0191], antibodies to Nup153 [paragraphs 0051, 0160], functional nucleic acids including antisense molecules, aptamers, ribozymes, triplex forming molecules, external guide sequences [paragraph 0087], RNA interference molecules (RNAi) small interfering RNA (SiRNA) [paragraph 0092], small molecules [paragraph 0192], flavenoids [paragraph 0194] and synthetic peptides [paragraph 0359].

In addition to the extensive guidance on how to make inhibitors, the specification provides extensive guidance on screening for the inhibitors of nuclear envelope breakdown. In

particular, the section of the application titled "Methods of Identifying and Screening" [paragraph 0267] discloses an extensive variety of tests for inhibition. Such methods are described in additional detail in Example 1.

Accordingly, there is extensive guidance on the types of compounds that may be used as inhibitors, the regions of Nup153 that could be targeted for inhibition and how to test these compounds for inhibitory activity.

Given these teachings, one of ordinary skill in the art could, for example, refer to the guidance on the importance of the zinc finger structural region of Nup153, make a peptide inhibitor of Nup153 based on this guidance and then test the inhibitor in an assay for Nup153 inhibition.

The Quantity of Experimentation

The Examiner has argued that a large quantity of experimentation would be necessary to determine if the administration of peptide based Nup153 inhibitors *in vivo* would be effective in inhibiting cell cycle progression. The MPEP section 2164.04 provides guidance on the amount of experimentation in an enablement determination stating that:

> "The test is not merely quantitative since a considerable amount of experimentation is permissible if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed".

Applicants have commented above on the extensive guidance provided in the specification as to the direction in which experimentation should proceed. In particular, the

application teaches that an inhibitor must inhibit Nup153, which can readily be determined by the assays in the application. It would be a routine matter to make inhibitors given the teaching in the specification regarding the structure of Nup153 and its interaction with COPI.

Once a compound is prepared, the *in vitro* assays described in the specification can be used to test for inhibition. The Examiner has argued on page 7 of the Action that the question is not how to make and administer the therapeutic peptides but whether the administration of the peptides which inhibit Nup153 *in vivo* would be effective in inhibition of cell cycle progression and cell proliferation and in treatment of cancer. Additional guidance regarding *in vitro* studies is provided by *Cross v. Iizuka*, 753 F.2d 1040, 105 0, 224 USPQ 739, 747 (Fed. Cir. 1985), which is cited in the MPEP Section 2164.02:

> "[B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence." (Citations omitted.)

Applicants submit that in the present application there is a direct correlation between the demonstrated *in vitro* inhibition of nuclear envelope breakdown which is a fundamental requirement for the progression of the cell cycle and the *in vivo* of inhibition of the cell cycle. Based on the pharmacological activity of a Nup153 inhibitor in inhibiting nuclear envelope breakdown a rigorous correlation, in particular *in vivo* data or clinical data is not required to satisfy the enablement requirement. Also, a drug candidate is the subject of an IND which has been accepted by the FDA and are currently being studied in human clinical trials.

In summary Applicants submit the specification is enabling under an *In re Wands* analysis for each of the reasons presented above on how to make compounds that function as inhibitors and test these compounds in a variety of assays in particular the assay methods described in Example 1.

35 U.S.C. §112 First Paragraph Rejections – Written Description

The Examiner has rejected claims 50, 64-67 and 75-80 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

In presenting this rejection, the Examiner identified certain factors that are pertinent in determining if the written description requirement has been satisfied: the disclosure of complete or partial structure, physical and chemical properties, functional characteristics, structure/function correlation and methods of making the claimed invention and any combination of these factors.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession

of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem*, 323 F.3d at 963, 63 USPQ2d at 1613. An application specification may show actual reduction to practice by describing testing of the claimed invention or, in the case of biological materials, by specifically describing a deposit made in accordance with 37 CFR 1.801 *et seq.* See *Enzo Biochem*, 323 F.3d at 965, 63 USPQ2d at 1614.

The Applicants respectfully traverse this rejection and, in line with the factors identified by the Examiner, provide the following discussion.

Disclosure of Complete or Partial Structure

The Applicants disclosed a nucleic acid and protein sequence for Nup153 [paragraph 0056]. Furthermore, the Applicants have described the structure of Nup153 and important structural features of the protein. The structure of Nup153 can be divided into three regions – a unique N terminal region, a central domain consisting of four or five zinc fingers (depending on species) and a C terminal region containing approximately 30 irregularly spaced FXFG repeats [paragraph 0037]. Given the identification of the zinc finger region, the Applicants provide

possible constructs which include two or more zinc fingers [see paragraph 0044-0050]. These possible constructs, along with the descriptive portions on calculating homology and identifying acceptable amino acid substitutions and modifications [see paragraphs 0055-0056 and 0140-0149], are teachings as to the structure of Nup153 inhibitors. In particular, the Applicants have provided extensive description on the important structural regions of Nup153 and have provided, in particular, a working example with an inhibitor that utilizes one of these structural regions –a fragment containing the zinc finger region (see paragraphs 0036-0038, Fig. 7 and Exhibit 1). Applicants also have presented a peptide sequence isolated by its ability to bind the zinc finger region of Nup153, which functions as an inhibitor of Nup153 (Example 2).

Therefore, the Applicants respectfully submit that the Applicants' disclosure of the structure of Nup153 and inhibitory function based on this structure satisfies as a pertinent factor in meeting the written description requirement.

Structure Function Correlation

Applicants have described structure–function relationships, generally, and have disclosed specific examples of these correlations. In particular, Applicants have provided working examples specifically demonstrating a fragment encompassing the central zinc finger domain of Nup153 functions as an inhibitor [paragraph 0038, Fig. 7, Example 1].

The zinc finger regions are an important structure related to the function of Nup153 and, in Example 1, a fragment comprising the central zinc finger region of Nup153 was shown to

inhibit Nup153 [paragraph 0317]. This illustrates the correlation between the zinc finger structure and the function of inhibition.

As a further structure-function correlation, Applicants prepared antibodies specific to Nup153. Antibodies that specifically recognize Nup153 were used in a nuclear disassembly assay (one antibody recognized the zinc finger region and the other the N terminal region) and both antibodies were able to prevent the normal progression of events in disassembly illustrating the functional importance of these regions in the function of Nup153 [paragraph 0161 and paragraph 0318].

Also, Applicants described using the zinc finger domain of Nup153 to select for peptides that inhibit nuclear envelope breakdown. This resulted in the isolation of CTHPFTHECGGGS (SEQ ID NO: 30) in Example 2 which was able to inhibit nuclear envelope breakdown [paragraphs 0357-0360].

Accordingly, Applicants have identified structure-function correlations in inhibitors based on a fragment of Nup153 itself, and inhibitors based on the preparation of compounds (an antibody and a peptide) which inhibit Nup153. Given the description of three different types of inhibitors-the Nup153 fragment, the antibody and the peptide, the Applicants respectfully submit to have satisfied the structure-function correlation as a pertinent factor in meeting the written description requirement.

Method of making the claimed invention.

Methods for making the claimed invention are provided throughout the specification [see paragraphs 0247-0266]. Given the disclosure in the application on Nup153, one of skill in the art

could readily make proteins, fragments, peptides and nucleic acid-based compounds to use in the methods of the invention.

In summary, Applicants submit that the elements for fulfilling the written description requirement are all present in the present specification, both individually and as suggested by the Examiner, in any combination thereof. As such, Applicants respectfully request allowance of the pending claims.

Supporting Documents

Applicants have cited the following documents in this Response and have attached them hereto as Appendix A:

> The Use of *Xenopus* Egg Extracts to Study Mitotic Spindle Assembly and Function *in vitro*, Desai, et al., Methods in Cell Biology, Volume 61, 1998, Pages 385-412, Chapter 20
>
> Microtubule Nucleating Capacity of Centrosomes In Tissue Sections, Salisbury, et al., (The Journal of Histochemistry & Cytochemistry, 1999 47(10) 1265-1273)
>
> Synthesis and Biological Evaluation of Myoseverin Derivatives: Microtubule Assembly Inhibitors, Chang, et al., (Journal of Medicinal Chemistry, 2001 44:26, 4497-4500)
>
> Learning About Cancer From Frogs: Analysis Of Mitotic Spindles In *Xenopus* Egg Extracts , Cross, et al., Dis Model Mech., 2009 Nov-Dec; 2(11-12):541-7

Request for Extension of Time

Applicants request that the time period for response be extended by three months to January 7, 2011. With this filing applicants authorize payment of the extension fee of $555.00 (small entity) pursuant to 37 CFR 1.17(a)(5). This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Should the Examiner have any questions regarding the pending patent application and/or present office action response, Applicants' attorney may be reached at the below-provided telephone number.

Respectfully submitted,

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APPENDIX A